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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/738,423	KING ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *113 and 115-125* is/are pending in the application.

4a) Of the above claim(s) *118 and 125* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *113, 115-117,119-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 7/20/2007, 10/24/2007, and supplemental response filed 8/7/2007 have been entered. Claim 113 has been amended. Claim 114 has been canceled. Claims 120-125 are newly submitted.

As an initial matter, it is noted in the supplemental response, the applicant's representative calls attention of a supervisory examiner. This request has been passed on to the supervisory examiner Woitach. It is noted the examiner's position has been reviewed by the supervisory examiner and a TC1600 practice specialist during the pre-appeal conference (see the Office communication mailed 5/18/2007), and the Office position has remains the same since.

It is noted the new claim 123 broadened the scope of the claims from a specific anti-cancer compound to any anti-cancer compound. Applicant is reminded that the elected invention (including the elected species) for examination in this application is drawn to a method of using attenuated tumor-targeted bacteria, and species election drawn to the combination of *Salmonella* and cisplatin. Hence, claim 123 would be examined to the extent that read on the elected species, i.e. cisplatin. Claim 125 is drawn to a non-elected species.

Claims 113, 115-125 are pending, however, claims 118, 125 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to

non-elected inventions, there being no allowable generic or linking claim. Claims 113, 115-117, 119-124 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 7/20/07 and 10/22/07 response would be addressed to the extent that they apply to current rejection.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/26/07 and 10/19/2007 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

However, the listed communications between the applicant and various patent offices for various U.S. and foreign patent applications are not suitable for publication on the face of the patent, and thus have been line through from the PTO1449.

Claim Objections

Claim 122 is objected to because it is a duplicate of claim 121.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 113, 116, 117, 119 stand rejected and claims 120, 123, 124 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Low et al* (Nat Biotech 1999;17:37-41, IDS), in view of *Schachter et al* (Cancer Biother Radiopharm 1998 Jun;13:155-64).

Low et al teach a method of treating tumor using a strain of *Salmonella* having disruption in msbB gene (msbB$^-$ mutant), said disruption reduces TNF-α induction (attenuated) and increases the LD_{50} of this pathogenic bacterium by 10,000-fold. The mutant *Salmonella* retains its tumor-targeting properties, i.e. exhibiting tumor accumulation ratios in excess of 1000:1 compared to its distribution in normal tissues. Administration of the msbB$^-$ *Salmonella* bacteria to melanoma-bearing mice results in reduced volume of solid tumors in the treated group compared to untreated controls (e.g. figs. 4, 5). *Low et al* conducted the test in mice, swine, human monocytes and mouse macrophages, and concluded that [the results] "HAVE BEEN CONSISTENT WITH THE NOTION THAT THE MSBB- BACTERIA CAN BE SAFE FOR USE IN HUMANS" (2nd paragraph, page 40). The teaching of *Low et al* differs from instant claims in that it does not explicitly teach

combining the bacteria therapeutic regimen with a chemotherapeutic agent such as cisplatin.

Schachter et al supplemented *Low et al* by disclosing a routine regimen of chemotherapy comprising cisplatin (a chemotherapeutic agent) for treating human melanoma, and establishing that it was well known in the art a combined drug therapy had been clinical routine since one single drug was insufficient for combating cancer. *Schachter et al* further supplemented *Low et al* by illustrating it was routine to combine a chemotherapeutic regimen with a newly developed biotherapy in treating solid tumors such as melanoma. *Schachter et al* presented a chemo-biotherapy protocol for patients with metastasis melanoma by including cytokines that regulate patients' immune system with conventional chemotherapy. *Schachter et al* applied the biotherapy and chemotherapy sequentially, i.e. modulating a patient immune system before or after the chemotherapy. Accordingly, it would have been obvious to the skilled in the art to combine the newly developed bacteria therapy with a conventional chemotherapy and to administer such in a sequential manner (not concomitantly).

The rationale for the design of the combined therapy was to achieve a higher percentage of a complete response (CR, meaning disappearance of all measurable disease) to drug treatment. *Schachter et al* teach that conventional chemotherapy such as a 4-drug regimen (BCNU, DTIC, **cisplatin** and tamoxifen) could have 40-50% response rate in patients being treated, but only 10-14% of patients achieved a complete response. When using the chemo-biotherapy, the response rate was 50%, and the complete response rate was up to 22%. *Schachter et al* do not specifically

teach the tumor-targeted bacteria, but illustrated the need of further improvement of the conventional chemotherapy.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply newly developed therapeutic means in the art and combine such with a routine anti-cancer drug regimen, and it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the attenuated tumor-targeted mutant *Salmonella* therapy as taught by *Low et al* with a routine chemotherapeutic regimen as taught by *Schachter et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for maximal therapeutic effects. Given the state of the art that the conventional therapy alone was often insufficient in combating cancer, given the skilled was constantly searching for new means to improve cancer treatment, and given that each of the cited references teaches an agent that is effective in cancer therapy, one would have had a reasonable expectation of success when combining the two. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

1. The applicant argues, "the prior art does not each every claim limitation".

In response, the limitation of administering cisplatin was taught by *Schachter et al;* and the limitation of administering *Salmonella* msbB- mutant was taught by *Low et al*;

and the motivation to combine more than one therapeutic means was clearly illustrated by *Schachter et al.* Hence, the cited prior art taught each and every claim limitation.

The applicant then asserts the issue is that there has not been a specific line of legal reasoning that bridges Low's modification by Schacheter to arrive at the specific claim limitation to combine only cisplatin with attenuated tumor-targeted Salmonella.

In response, as an initial matter, it is noted cisplatin is the elected species, and hence specifically mentioned in the rejection. However, the claims, particularly new claim 123 are not limited only to the combination of cisplatin and attenuated *Salmonella*, but any anti-cancer chemicals.

As to a specific line of legal reasoning, "AN EXPRESS SUGGESTION TO SUBSTITUTE ONE EQUIVALENT COMPONENT OR PROCESS FOR ANOTHER IS NOT NECESSARY TO RENDER SUCH SUBSTITUTION OBVIOUS". In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). It was indicated previously, "FINDING OF OBVIOUSNESS DOES NOT REQUIRE EXISTENCE OF EXPRESS, WRITTEN MOTIVATION TO COMBINE IN PRIOR ART, SINCE MOTIVATION TO COMBINE MAY BE FOUND IN NATURE OF PROBLEM TO BE SOLVED, LEADING INVENTORS TO LOOK TO REFERENCES RELATING TO POSSIBLE SOLUTIONS TO THAT PROBLEM". (*Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686 CA FC 2004). Also, "FINDING OF MOTIVATION TO COMBINE PRIOR ART REFERENCES NEED NOT BE SUPPORTED BY SHOWING THAT CLAIMED COMBINATION IS *PREFERRED OVER OTHER ALTERNATIVES*, SINCE PROPER INQUIRY IS WHETHER THERE IS SOMETHING IN PRIOR ART AS WHOLE TO SUGGEST DESIRABILITY, AND THUS OBVIOUSNESS, OF MAKING COMBINATION, NOT WHETHER THERE IS SOMETHING IN PRIOR ART AS WHOLE TO SUGGEST THAT COMBINATION IS PREFERRED OR MOST DESIRABLE. (*In re Fulton*, 73 USPQ2d 1141 CA FC 2004). Hence, even though *Schachter et al* did not teach combining specifically the cisplatin and the attenuated

Salmonella, both *Low et al* and *Schacheter et al* teach new means of treating cancer, particularly melanoma, it would have been obvious to the skilled artisan to look for any new means and combining such with existing therapeutic means according to the nature of the problem to be solved, i.e. treating solid tumor cancer. Again, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980), wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art compositions of cisplatin and attenuated *Salmonella*-all taught to be useful for the treatment of cancer, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of cancer with a reasonable expectation of success.

In response to the argument that there is no specific suggestion or teaching in the references to combine prior art, KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a fining of obviousness. See the recent Board decision *Ex parte Smith*, -- USPQ2d--, slip op.at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Here, all the recited elements were known in the art, and hence "THE COMBINATION OF FAMILIAR ELEMENTS ACCORDING TO KNOWN METHODS IS LIKELY TO BE OBVIOUS WHEN IT DOES NO MORE THAN YIELD PREDICTABLE RESULTS." *KSR,* 127 S. Ct. at 1740, 82 USPQ2d at 1395-96. Accordingly, the claimed

invention as a whole was *prima facie* obvious.

2. The applicant argues "the rationale supporting the rejection is "Obvious to try" and no more.

It is noted the BPAI stated "THE SUPREME COURT RECENTLY CAST DOUBT ON IN RE DEUEL TO THE EXTENT THE FEDERAL CIRCUIT REJECTED AN OBVIOUS TO TRY TEST", "UNDER KSR, IT'S NOW APPARENT 'OBVIOUS TO TRY' MAY BE AN APPROPRIATE TEST IN MORE SITUATIONS THAN WE PREVIOUSLY CONTEMPLATED" *Ex Parte Kubin* USPQ2d (BPAI May 31, 2007).

Here, the Applicants argue the examiner relied on Schachter for a general desirability to try new combinations to treat cancer by combining entirely different fields of therapy.

In response, the bacteria therapy has been proven effective in treating melanoma by *Low et al*, and the cisplatin has been proven effective in treating melanoma as shown by *Schachter et al*. They are apparently not entirely different fields of therapies. They both were proven effective options available in the art for treating melanoma. The court has held "ARGUMENT THAT TWO REFERENCES ARE NONANALOGOUS IS WITHOUT MERIT WHERE BOTH ARE CONCERNED WITH IDENTICAL FIEDL OF ENDEAVOR". *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Hence, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these therapeutic options to generate a new regimen for the treatment of cancer.

3. The applicant argues "Examiner's proposed modification alters the principle underlying Schachter's therapy and would render it unsatisfactory for its intended use".

In this section, the applicants basically argue that in order to combine the cited references, the bacteria disclosed by *Low et al* has to substitute the effect of the biotherapy taught by *Schachter et al*, and the cisplatin alone has to be able to replace the four-drug regimen.

In response, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Also, "IT IS NOT NECESSARY THAT THE PRIOR ART SUGGEST THE COMBINATION TO ACHIEVE THE SAME ADVANTAGE OR RESULT DISCOVERED BY APPLICANT". See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) Here, the Office does not suggest that the attenuated bacteria is an equivalent of cytokines used by *Schachter et al*, rather, *Schachter et al* is relied on for a general desirability of combining a new therapeutic regimen with an existing conventional one, such as an anti-cancer chemical compound. In a clinical setting, the skilled rarely uses only one drug/one type of therapy in a cancer therapeutic regimen, particularly when the therapeutic approach is relative new to the field. The prior art is replete with combination therapies combining chemotherapy with radiotherapy or newly developed cytokine, bacteria, gene therapy (*Schachter et al* was only one of many), particularly when the subject of the treatment is a human subject, and the publication was not pure investigation on a new approach in animal models as did by *Low et al*.

Even assuming, *arguendo*, one has to substitute the biotherapy with a therapy having the same underlying principle, the biotherapy taught by *Schachter et al* is for priming and immune regulation. To this end and in direct rebuttal of the applicant's argument, there was evidence in the prior art showing that attenuated *Salmonella* does have priming and immune regulation effect. *Jirillo et al* (Int J Immunopharmacol 1986;8:881-6) teach that attenuated *Salmonella* bacteria enhances immune responsiveness in patients with gynecologic malignancies via immune regulation (see e.g. the abstract). Thus, attenuated *Salmonella* does have similar underlying principle as does the biotherapy in treating cancer. Accordingly, the claimed invention as a whole was *prima facie* obvious.

4. Applicant asserts the claimed invention may be compared with prior art that is closer than that applied by examiner.

It is noted the applicant did not introduce any new art closer than that applied in the rejection. Since both cited art taught treating a solid tumor cancer, melanoma, they are close related arts, and both show effects of suppressing cancer, and thus one would reasonably expected an enhanced anti-cancer effect when combining them compared to any single method alone.

Moreover, the new claim 23 is not limited to any particular anti-cancer compound, which made the prior argument drawn to specific drug combinations moot.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claim 115 stands rejected, and claims 121, 122 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Low et al* (Nat Biotech 1999;17:37-41, IDS), in view of *Schachter et al* (Cancer Biother Radiopharm 1998 Jun;13:155-64) as applied to claims 113, 116, 117, 119, 120, 123, 124 above, further in view of *Pawelek et al* (Cancer Res 1997;57:4537-44, IDS), for reasons of record and set forth *supra*.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QL
December 17, 2007